UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/320,767	05/27/1999	NICK GIANNOUKAKIS	A32362	5337

21003 7590 12/18/2002

BAKER & BOTTS
30 ROCKEFELLER PLAZA
NEW YORK, NY 10112

EXAMINER
ANGELL, JON E

ART UNIT	PAPER NUMBER
1635	18

DATE MAILED: 12/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/320,767	GIANNOUKAKIS ET AL.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,21-24 and 27-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,21-24 and 27-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 May 1999* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This Action is in response to the communication filed on 10/1/02 as Paper No. 17. Claims 20, 25 and 26 have been cancelled without prejudice. Claims 1-12, 21-24, and 27-30 are pending in the application and are examined herein. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

2. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action.

Drawings

3. In order to avoid abandonment, the drawing objections noted in form PTO 948 (Notice of Draftsperson's Patent Drawing Review) mailed on 1/4/2000, must now be corrected. Corrections can only be effected in the manner set forth in the above noted form. It is noted that the objection will not be held in abeyance. Corrected drawings must be submitted in response to this Office Action in order to avoid abandonment (see attached).

Claim Rejections - 35 USC § 112, first paragraph

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 5-7, 21-24 and 27-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons of record, and in addition for the reasons set forth below.

It is respectfully pointed out that the claims are drawn to a method of reducing ***any*** beta-cell dysfunction (including Fas-mediated beta cell apoptosis) by administering ***any*** inhibitor of IL-1beta activity. The genus of inhibitors encompassed by the claims includes any molecule encoded by a nucleic acid that can inhibit any activity of IL-1beta (e.g. Fas-mediated beta-cell apoptosis) including antisense molecules, dominant negative polypeptides, decoy receptors, transcription factors, etc.

First, with regard to the treatment of ***any*** beta-cell dysfunction, it is pointed out that although the intended use of the method (based on the disclosure in the specification) is for the treatment of beta-cell dysfunction as it pertains to only dysfunctional insulin production and/or secretion (e.g. diabetes), the claims are not so limited and encompass the treatment of any beta-cell dysfunction including beta-cell carcinoma--also known as insulinoma (see ***Pelengaris,*** Endo. Rel. Cancer 8:307-314; 2001). As mentioned above, there is no indication in the specification or the prior art that administration of any inhibitor of IL-1beta activity or Fas mediated apoptosis would result in the reduction of insulinoma.

Second, with respect to the inhibitors disclosed as they pertain solely to the treatment of diabetes (or diabetes-related dysfunctions), the claimed genus of inhibitors encompasses potentially millions of different species considering the claims encompass molecules (i.e. inhibitors) that can act anywhere in the IL-1beta pathway and includes antisense molecules. The written description guidelines indicate that the description requirement for a claimed genus may

be satisfied through sufficient description of a representative number of species, by actual reduction to practice, by disclosure of relevant identifying characteristics (i.e. structure or other physical and/or other chemical properties), by disclosure of functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics sufficient to show applicant was in possession of the claimed genus." (See MPEP 2100-164). Regarding the description of a representative number of species, the guidelines note "a satisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the applicant was in possession of the **necessary common attributes or features of the elements possessed by the members of the genus** in view of the species disclosed." (Emphasis added; see: Federal Register: December 21, 1999, Volume 64, Number 244; revised guidelines for written description). In the instant case, no common attributes or features possessed by the inhibitors are disclosed. There is no indication of any relevant common structural/chemical characteristics, and no identification of any structural limitations/requirements which provide guidance on the identification of molecules that meet the functional limitations.

With respect to the disclosure in the specification of a method for identifying any species encompassed by the claims, it is noted that MPEP 2163 indicates,

> "The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence."

The method disclosed to identify any inhibitor merely identifies the claimed molecules by function. There is no indication in the specification or the prior art teaching the relationship between the structure of the inhibitors and their function.

Response to Arguments

6. Applicant's arguments have been fully considered but they are not persuasive.

Applicants assert that the essential feature of the present invention is based the discovery that the inhibition of IL-1beta activity or Fas mediated apoptosis, reduces beta cell dysfunction, thus the invention relates to methods of reducing beta-cell dysfunction (see pages 3-4 of the response filed 10/1/02). Therefore, Applicant's contend, any nucleic acid molecule capable of encoding an inhibitor of IL-1beta or Fas mediated apoptosis may be utilized to reduce beta-cell dysfunction. Applicants argue that the working examples teach two such molecules: IL-1Ra (also known as IRAP) and IGF-1, and that the specification indicates a number of inhibitors of IL-1beta activity and a number of inhibitors of Fas mediated apoptosis (see page 4 of the response filed 10/1/02). Applicants also assert that the specification clearly indicates a method of identifying such inhibitors.

In response to Applicant's arguments, it is acknowledged that the specification indicates by working example only two inhibitors of IL-1beta (IRAP and IGF-1) and that the specification names a number of inhibitors including dominant negative mutant forms of Fas or FADD protein and members of the bcl-2 family of proteins, and also indicates a method of identifying any potential inhibitors.

It is pointed out that in the instant case, no common attributes or features possessed by the inhibitors are disclosed. There is no indication of any relevant common structural/chemical

characteristics, and no identification of any structural limitations/requirements which provide guidance on the identification of molecules that meet the functional limitations, such as antisense molecules. Regarding the applicant's assertion that that a method of identifying any inhibitor is included in the specification, it is noted that the method disclosed merely identifies the claimed molecules by function. There is no indication in the specification or the prior art teaching the relationship between the structure of the inhibitors and their function.

Therefore, the specification does not provide an adequate written description of the genus of inhibitory molecules considering the vast number of species encompassed by the claims (including antisense inhibitors), and the lack of disclosure identifying the common attributes or features possessed by the members of the genus.

7. In view of the reasons set forth in the written description rejection above, and additionally for the reasons below, claims 1-12, 21-24 and 27-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reducing beta-cell apoptosis comprising directly administering a nucleic acid molecule encoding a protein inhibitor of IL-1beta activity to a beta-cell whereby expression of said nucleic acid molecule results in reduction of beta cell apoptosis, does not reasonably provide enablement for reducing any beta-cell dysfunction (including Fas-mediated apoptosis) by general (e.g. systemic) deliver of the therapeutic nucleic acid to beta-cells in vivo. Furthermore, claims 9-12 are only enabled for an isolated mammalian beta cell comprising a nucleic acid molecule, wherein said

nucleic acid molecule comprising and expressing a protein inhibitor of IL-1beta activity, wherein the expression of said protein inhibitor of IL-1 beta activity reduces beta-cell apoptosis.

The instant claims are drawn to a method of reducing any beta-cell dysfunction (including Fas-mediated beta-cell apoptosis) comprising introducing a nucleic acid molecule encoding an inhibitor of IL-1beta into a beta cell whereby expression of said nucleic acid molecule results in reduction of beta-cell dysfunction. Additionally, claims 9-12 are drawn to a mammalian beta-cell comprising a nucleic acid expressing an inhibitor of IL-1beta activity, wherein the beta-cell may be either in vitro or in vivo.

It is respectfully pointed out that the claims do not indicate that the transfected beta-cells are transplanted into a subject; therefore, the claims are limited to in vitro and in vivo embodiments only (i.e. administering the therapeutic nucleic acid to cells in vitro and to cell sin vivo) and do not encompass the ex vivo administration of the transfected beta cells to a subject. It is acknowledged that the originally filed claims were limited to the ex vivo administration of the transfected cells; however, the claims were amended to remove the steps comprising the transplantation of the transfected beta-cells (see communication filed 4/9/01 as Paper No. 10) prior to the request for a Continued Prosecution Application (CPA). Therefore, the instant claims are limited to the in vitro and in vivo reduction of beta-cell dysfunction and Fas-mediated beta-cell apoptosis and do not encompass any ex vivo embodiments.

It is noted that based on the specification (and declaration), an essential feature of the invention is that the mammalian beta cell is isolated, transfected and transplanted in order to practice the claimed invention. Therefore, the invention is only enabled for the method and cell wherein the mammalian cell is an isolated mammalian beta cell.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

First, with regard to the treatment of ***any*** beta-cell dysfunction, it is pointed out that although the intended use of the method (based on the disclosure in the specification) is for the treatment of beta-cell dysfunction as it pertains to only dysfunctional insulin production and/or secretion (e.g. diabetes), the claims are not so limited and encompass the treatment of any beta-cell dysfunction including beta-cell carcinoma--also known as insulinoma (see ***Pelengaris et al.*** Endo. Rel. Cancer 8:307-314; 2001). There is no indication in the specification or the prior art that administration of any inhibitor of IL-1beta activity or Fas mediated apoptosis would result in the reduction of insulinoma. Furthermore, Pelengaris teaches "Insulinomas are tumors of the islets of Langerhans and may encompass different forms of beta cell disease, all of which produce hyperinulinism and hypoglycemia" (see p. 307, column 1); and, "expression of the anti-apoptotic protein Bcl-2 has been reported in one-third of human insulinomas, suggesting that the suppression of apoptosis may contribute to the initiation, progression, or both, of these tumors" (see page 310, second column). Therefore, one of skill in the art would not expect any inhibitor

or IL-1beta or Fas-mediated apoptosis to be able to treat *any* beta-cell dysfunction such as insulinoma.

Nature of the Invention:

As mentioned above, the claims are drawn a beta cell comprising a vector which expresses an inhibitor of IL-1beta activity (wherein the cell is either in vitro or in vivo), and to the treatment of beta-cell dysfunction and encompass the in vitro and in vivo administration of a therapeutic nucleic acid encoding an inhibitor of IL-1beta. The only use contemplated in the specification for the beta cell expressing exogenous inhibitor of IL-1beta activity is for the reduction of beta cell dysfunction. Therefore, the nature of the invention is gene therapy for the treatment of any beta-cell dysfunction.

Breadth of the Claims:

The independent claims are very broad and encompass the treatment of any beta-cell dysfunction (or Fas-mediated beta-cell apoptosis) by administering a vector that comprises and expresses any inhibitor of IL-1beta, wherein the said vector is administered to beta cells in vitro or in vivo. It is noted that administering the therapeutic nucleic acid to the beta cells in vivo encompasses systemic administration of the therapeutic nucleic acid. Examples of beta-cell dysfunctions include Type I diabetes or Type II diabetes (including all symptoms associated with these types of diabetes including apoptosis, insulin production, insulin secretion, and insulin resistance) and insulinoma (i.e., beta cell carcinoma—and all symptoms thereof including unregulated proliferation, imortalization, hypoglycemia, insulinitis, etc.). Therefore, given the broadest reasonable interpretation of the claims, the invention encompasses the treatment of any

of the stated beta-cell disorders by administering a nucleic acid that expresses any inhibitor of IL-1beta.

The state of the prior art and unpredictability of the art:

As mentioned above, the claims are very broad and encompass gene therapy treatment of any beta-cell dysfunction, such as diabetes or insulinoma, by administering a therapeutic nucleic acid that expresses an inhibitor of IL-1beta.

Regarding gene therapy as a whole, the art at the time of filing considered gene therapy to be unpredictable as modes of delivery that would provide efficient expression of genes encoding the therapeutic polypeptide sufficient to provide an alleviation of symptoms related to the target disease or condition had not been developed. Currently, the state of the art of gene therapy is still in its infancy as the art is plagued by unpredictability. For instance, Anderson (Nature 392:25-30; 1998) teaches, "Except for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene therapy protocol has been successful in the treatment of a human disease... the reason for the low efficiency of gene transfer and expression in human patients is that we still lack a basic understanding of how vectors should be constructed, what regulatory sequences are appropriate for which cell types, how in vivo immune defenses can be overcome and how to manufacture efficiently the vectors we do make."

Specifically regarding gene therapy for diabetes, Levine (Mol. Med. Today 5:165-171; 1999) indicates many of the obstacles that need to be overcome in order to create an effective gene therapy for diabetes including gene transfer problems, cell transfer problems, and the responsiveness of the transduced beta-cells to blood glucose levels.

Regarding gene transfer into beta cells, Levine indicates that there are two general means by which therapeutic genes can be introduced into beta cells: by transducing the islet cells ex vivo and reintroducing the cells in vivo (see p. 165, last paragraph), and transfer of the therapeutic gene(s) into beta-cells in vivo. However, Levine also indicates, "Successful islet cell transplantation has proved to be an elusive goal... (and) to date, there are no studies demonstrating that [in vivo gene transfer into beta-cells] can be done." (See p. 166).

Levine teaches that both type I and type II diabetes results in the apoptotic death of beta-cells (see p. 166-167) and further indicates that preventing beta-cell apoptosis may be potentially applicable to both type I and type II diabetes (see p. 168, first column) either by inhibiting apoptosis of beta cells before they die by transfer of anti-apoptotic genes such as Bcl-2 into the beta cells, by regenerating beta cells, or by transplanting new/replacement cells for the beta cells (see p. 168-169). However these methods can not be predictably reproduced for several reasons including: the transfer in vivo delivery of the therapeutic nucleic acid to the specific target cells (see Anderson as mentioned above), regeneration does not continue over long periods of time (see Liu p. 168, third column), and transplantation of cadaveric human islet cells has been disappointing in terms of achieving insulin independence largely because of the inability to obtain large quantities of the cells (see Liu, p. 168, column 2).

Levine also indicates that successful gene transfer into beta cells (either in vivo or ex vivo) and/or successful cell transplant are not the only obstacles to obstacle to overcome in order to effectively treat diabetes. Once the therapeutic gene(s) or cells are successfully delivered, the cells must be able to respond changes in blood glucose levels:

> "A definitive treatment for diabetes mellitus will be one that maintains a normal blood glucose concentration in the face of fluctuating dietary intake. To accomplish this there

must be mechanisms to sense the amount of blood glucose coupled to rapid release of the right amount of insulin." (See p. 165, abstract).

Therefore, any successful therapy for diabetes must allow the insulin producing cells to be responsive to the fluctuations of blood glucose levels, a demonstration not present in the instant specification.

Levine summarizes the state of gene therapy for diabetes by stating, "the ultimate goal of a definitive, permanent treatment of diabetes through gene therapy lies in the distant future." (p. 170, last paragraph).

Working Examples and Guidance provided:

The working examples and guidance provided in the specification (and declaration, see below) were indicated fully in a previous Office Action, and are summarized here. The only working examples presented encompass expressing an inhibitor of IL-1beta (specifically, either IL-1Ra/IRAP or IGF-1) in a mouse beta cell in vitro, followed by the transplantation of the beta cell into a mouse model for Type I diabetes. The results present only indicate that the transplanted beta cells had a reduced incidence of apoptosis (see declaration). There is no evidence presented indicating that the methods used resulted in a definitive, permanent treatment of diabetes.

Quantity of Experimentation:

Considering the number of obstacles recognized in the art which must be overcome for successful gene therapy treatment for beta-cell dysfunction (see above) and the fact that the only evidence presented is the transplantation beta-cells which express exogenous IL-1Ra/IRAP or IGF-1, which results in a reduction in the incidence of beta-cell apoptosis. There is no indication that the therapeutic nucleic acids can be delivered to beta cells by in vivo administration of the

nucleic acid, nor is there any indication that the cells expressing the inhibitory molecules are sensitive and responsive to fluctuating blood glucose levels—a requirement for definitive, permanent treatment of diabetes. Therefore, more experimentation is required in order to overcome the remaining obstacles for the treatment of beta-cell dysfunction.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the high degree of unpredictability of gene therapy for diabetes recognized in the art, the breadth of the claims, the lack of working examples and guidance provided, and the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed method is undue.

Response to Arguments/Declaration

8. The declaration under 37 CFR 1.132 filed 10/1/02 is insufficient to overcome the rejection of claims based upon the lack of enablement for the in vivo embodiments of the claims under 35 U.S.C. 112, first paragraph as set forth in the previous Office Action and above because the declaration only presents evidence that beta cells transfected in vitro with a modified Ad vector or lentiviral encoding/expressing IRAP and transplanted into a NOD mouse (and a NOD SCID mouse) results in the reduction of beta-cell apoptosis. However, as mentioned above, the claims currently do not indicate that the beta-cells expressing the exogenous inhibitors are transplanted into a subject. Therefore, the claims do not encompass ex vivo embodiments such as those presented in the declaration. Furthermore, it is pointed out that the art currently recognizes a number of problems related to gene therapy of beta-cell dysfunction, regardless if the treatment

is in vivo or ex vivo, which have not been overcome by the evidence presented. For example, there is no evidence presented that the transfected beta cells are responsive to fluctuations of blood glucose levels.

Claim Rejections - 35 USC § 112, second paragraph

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 5-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Method claims require an active or positive step that accomplishes the goals for the method which were stated in the method's preamble. The instant claims lack such a step and are confusing because the additional method step(s) is not sufficiently set forth. While minute details are not required in method claims, at least the basic steps must be recited in a positive, active fashion. See Ex parte Erlich, 3 USPQ2d1011, p.1011 (Bd. Pat. App. Int. 1986). The specific problem with the instant claims is the claims are drawn to a method of reducing Fas-mediated beta-cell apoptosis; however, there is no requirement or active or positive step in the claims indicating that Fas-mediated beta cell apoptosis is actually reduced. This is indefinite because it leaves the scope of the claim unclear as to whether it is required that method actually reduces Fas-mediated beta-cell apoptosis.

Amending claim 5 to indicate the claim is drawn to a method of reducing beta-cell dysfunction or indicating that expression of the nucleic acid results in reduction of Fas-mediated beta-cell apoptosis would obviate this rejection.

11. Claims 9-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant claims are drawn to a mammalian beta cell comprising a recombinant nucleic acid molecule encoding an inhibitor of IL-1beta activity wherein expression of the inhibitor reduces beta-cell dysfunction. The claims are indefinite because it is unclear if the method reduces dysfunction of the beta cell comprising the nucleic acid molecule (i.e. reduces dysfunction of the transfected cell itself), or if the method reduces the dysfunction of a different beta-cell (i.e. a beta cell other than the transfected cell).

Amending claim 9 to indicate that reduction of beta-cell dysfunction is limited to the beta cell comprising the nucleic acid molecule encoding the IL-1beta inhibitor would obviate this rejection.

12. Claims 23 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant claims are indefinite because they depend on claim 20. Claim 20 has been cancelled (see Paper No. 20, filed 7/10/00), thus rendering dependent claims 23 and 24 indefinite.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 1, 5, 8, 9 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Liu et al. (Human Gene Therapy 7:1719-1726; 1996).

Claim 1 is drawn to the a method of reducing b-cell dysfunction comprising introducing a nucleic acid molecule encoding an inhibitor of IL-1 beta into a beta cell. Claim 5 is drawn to a method of reducing Fas-mediated beta-cell apoptosis comprising introducing a nucleic acid molecule encoding an inhibitor of Fas mediated apoptosis into a beta cell. Claim 8 is drawn to the method of claim 5 wherein the inhibitor is a Bcl-2 family member. Claim 9 is drawn to a mammalian cell comprising a recombinant nucleic acid comprising and expressing an inhibitor or IL-1beta activity. Claim 22 is drawn to a recombinant herpes simplex viral (HSV) vector comprising a nucleic acid encoding an inhibitor of IL-1beta activity.

It is noted that the claims are very broad and encompass both in vitro as well as in vivo embodiments. The instant rejection is only directed to in vitro embodiments; specifically, the

embodiments wherein the nucleic acid is delivered to an isolated (i.e. in vitro) mammalian beta-cell.

Liu teaches a replication defective HSV-1 vector comprising an inhibitor of IL-1beta activity (specifically, the inhibitor is Bcl-2; p. 1720, Figure 1). Liu teaches a mammalian cell (specifically, a human or mouse islet cell) comprising the HSV-1 vector which comprises and expresses Bcl-2 (see p. 1724, Figure 4A). Liu also teaches a method of using the HSV-1/Bcl-2 vector to inhibit cytokine-induced apoptosis. Liu specifically teaches that IL-1beta, IFN-gamma, and TNF-alpha were used in combination to induce apoptosis and cells transfected with HSV-1/Bcl-2 had reduced apoptosis (e.g., see p. 1724, Figures 4 and 5). Therefore, Liu clearly anticipates claims 1, 5, 8, 9 and 22.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 1, 5, 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. (Human Gene Therapy 7:1719-1726; 1996) in view of Yamabe et al. (BBRC 243:217-223; February, 1998).

The instant claims are drawn to a method of reducing beta-cell dysfunction (claim 1) (including Fas-mediated apoptosis; claim 5) by administering a nucleic acid encoding an inhibitor of IL-1beta activity (including a Bcl-2 family member; claim 8), and a mammalian beta-cell comprising a nucleic acid encoding an inhibitor of IL-1beta activity (claim 9).

It is noted that the claims are very broad and encompass both in vitro and in vivo embodiments. The instant rejection is only directed to in vivo embodiments; specifically the embodiments wherein the nucleic acid is directly delivered to an in vivo mammalian beta-cell.

Liu teaches a replication defective HSV-1 vector comprising an inhibitor of IL-1beta activity (specifically, the inhibitor is Bcl-2; p. 1720, Figure 1), and a mammalian cell (specifically, a human or mouse islet cell) comprising the HSV-1 vector which comprises and expresses Bcl-2 (HSV/Bcl-2) (see p. 1724, Figure 4A). Liu also teaches a method of using the HSV-1/Bcl-2 vector to inhibit cytokine-induced apoptosis. Liu specifically teaches that IL-1beta, IFN-gamma, and TNF-alpha were used in combination to induce apoptosis and mammalian beta-cells transfected with HSV-1/Bcl-2 exhibited reduced apoptosis (e.g., see p. 1724, Figures 4 and 5). Liu also teaches, "expression of Bcl-2 in pancreatic beta-cells may allow

for successful application of the immunoisolation approach to the treatment of diabetes." (See p. 1725, middle of first column).

Liu does not explicitly teach that the nucleic acid can be directly delivered to mammalian beta-cells in vivo for the reduction of beta-cell apoptosis.

Yamabe teaches a method of preventing hypoxic liver cell necrosis by directly delivering a vector comprising a nucleic acid which encodes and expresses human Bcl-2 protein to an in vivo rat liver cell (e.g. see p. 217, abstract; p. 218, under "in vivo gene transfection"; and p. 220-222, under "Transfection of hbcl-2 prevents liver dysfunction").

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of invention to combine the teachings of Liu and Yamabe and create a method of reducing beta cell dysfunction in vivo (including Fas-mediated apoptosis), by directly administering a nucleic acid encoding bcl-2 to mammalian beta-cells in vivo. The motivation to do so would have been for the treatment of diabetes, as indicated by Liu.

18. Claims 27 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Welling et al. (Human Gene Therapy 7:1795-1802; 1996) in view of Amalfitano et al. (J. Virol. 72:926-933; February, 1998).

Claim 27 is drawn to a recombinant E1 and E3 deleted adenoviral vector comprising a nucleic acid sequence encoding an inhibitor of IL-1beta activity. Claim 30 is drawn to a recombinant adenoviral vector comprising an adenovirus E3 region modification and a nucleic acid encoding an inhibitor of IL-1beta.

Welling teaches a recombinant adenoviral vector comprising a nucleic acid sequence encoding an inhibitor of IL-1beta activity wherein the inhibitor of IL-1beta activity is IL-1Ra (also known as IRAP) (for example seep. 1795 abstract). Welling indicates that the vector was capable of delivering and expressing IL-1Ra in rat skeletal muscle capillary endothelium and muscle fibers during vascular isolation of the hindlimb (see p. 1795, first column). Welling also teaches that IL-1Ra is "a clinically important inhibitor of IL-1's deleterious actions in shock, inflammation and rheumatoid arthritis." (See p. 1796, second column). Welling also indicates that "adenoviral transduction of the lung and liver is associated with an inflammatory reaction with a lymphocytic infiltrate and necrosis" (See p. 1800, second column); and "Transient IL-1Ra expression might be applicable to the prevention of sepsis-induced acute respiratory distress syndrome or multiple organ dysfunction in which IL-beta is critical to disease pathogenesis" (see p. 1801, first column).

Welling does not teach that the adenoviral vector comprises E1 and E3 deletions or a modified E3 region.

Amalfitano teaches a recombinant adenoviral vector comprising deleted E1 and E3 gene functions (see p. 926, abstract). Regarding the E1/E3 deleted adenoviral vector, Amalfitano teaches, "The new vectors can be readily grown to high titers and have several improvements including an increased carrying capacity and a theoretical decreased risk of RCA (replication-competent Adenovirus)... The results suggest that the modified vectors may be very useful for both in vitro and in vivo gene therapy applications." (See p. 926, abstract).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to combine the teachings of Welling and Amalfitano to make an recombinant

E1/E3 deleted adenoviral vector comprising an inhibitor of IL-1beta, such as IL-1Ra/IRAP, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to combine the references and create the claimed vector because Amalfitano clearly indicates that the E1/E3 deleted adenoviral vector is an improved adenoviral vector. Specifically, Amalfitano teaches, "modified Ad vectors may have improved in vivo efficacy as a result of their decreased abilities to replicate and express multiple viral functions and/or epitopes." (See p. 926, last paragraph).

19. Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Welling et al. (Human Gene Therapy 7:1795-1802; 1996) in view of Parks et al. (PNAS 93:13565-13570; 1996).

Claim 28 is drawn to a recombinant adenoviral vector consisting essentially of adenoviral terminal repeats required for adenoviral replication and a nucleic acid sequence encoding an inhibitor of IL-1beta activity.

Welling teaches a recombinant adenoviral vector comprising a nucleic acid sequence encoding an inhibitor of IL-1beta activity wherein the inhibitor of IL-1beta activity is IL-1Ra (also known as IRAP) (for example seep. 1795 abstract). Welling indicates that the vector was capable of delivering and expressing IL-1Ra in rat skeletal muscle capillary endothelium and muscle fibers during vascular isolation of the hindlimb (see p. 1795, first column). Welling also teaches that IL-1Ra is "a clinically important inhibitor of IL-1's deleterious actions in shock, inflammation and rheumatoid arthritis." (See p. 1796, second column). Welling also indicates that "adenoviral transduction of the lung and liver is associated with an inflammatory reaction

with a lymphocytic infiltrate and necrosis" (See p. 1800, second column); and "Transient IL-1Ra expression might be applicable to the prevention of sepsis-induced acute respiratory distress syndrome or multiple organ dysfunction in which IL-beta is critical to disease pathogenesis" (see p. 1801, first column).

Welling does not teach that the adenoviral vector consisting essentially of adenoviral terminal repeats required for adenoviral replication.

Parks teaches a recombinant adenoviral vector consisting essentially of the cis-acting elements required for replication (i.e. the adenoviral terminal repeats (ITRs)) (see p. 13565, second column; and p. 13566, Figure 1). Parks also indicates that the adenoviral genes required for the "gutted" adenoviral vector to integrate, etc. are contained in a separate helper virus that expresses the trans acting factors.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to combine the teachings of Welling and Parks to make a modified recombinant adenoviral vector consisting essentially of the adenoviral terminal repeats required for adenovirus replication and a nucleic acid encoding an inhibitor of IL-1beta, such as IL-1Ra/IRAP, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to combine the references and create the claimed vector because Parks clearly indicates that the modified adenoviral vector consisting essentially of the adenoviral terminal repeats is an improved adenoviral vector. Specifically, Parks teaches the modified adenoviral vector has an increased cloning capacity, increased safety and reduced immunogenicity (see p. 13565, abstract).

20. Claims 29 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Welling et al. (Human Gene Therapy 7:1795-1802; 1996) in view of Kadan et al. (WO 96/18414, published June, 1996).

Claim 29 is drawn to a recombinant E2 and E4 deleted adenoviral vector comprising a nucleic acid sequence encoding an inhibitor of IL-1beta activity. Claim 30 is drawn to a recombinant adenoviral vector comprising an adenovirus E3 region modification and a nucleic acid encoding an inhibitor of IL-1beta.

Welling teaches an adenoviral vector comprising a nucleic acid sequence encoding an inhibitor of IL-1beta activity wherein the inhibitor of IL-1beta activity is IL-1Ra (also known as IRAP) (for example seep. 1795 abstract). Welling indicates that the vector was capable of delivering and expressing IL-1Ra in rat skeletal muscle capillary endothelium and muscle fibers during vascular isolation of the hindlimb (see p. 1795, first column). Welling also teaches that IL-1Ra is "a clinically important inhibitor of IL-1's deleterious actions in shock, inflammation and rheumatoid arthritis." (See p. 1796, second column). Welling also indicates that "adenoviral transduction of the lung and liver is associated with an inflammatory reaction with a lymphocytic infiltrate and necrosis" (See p. 1800, second column); and "Transient IL-1Ra expression might be applicable to the prevention of sepsis-induced acute respiratory distress syndrome or multiple organ dysfunction in which IL-beta is critical to disease pathogenesis" (see p. 1801, first column).

Welling does not teach that the recombinant adenoviral vector comprises a modified E2 and E4 gene region (claim 29) or a modified E3 region (claim 30).

Kadan teaches a recombinant adenoviral useful for gene delivery and expression wherein the adenoviral vector has been modified to reduce the host immune and inflammatory responses to the vector (e.g. see abstract). Specifically, Kadan teaches that the modified adenoviral vector "is free of all or a portion of the adenoviral E1 (including the E1a and E1b), E2, and E4 DNA sequences... (and) also include at least a portion of the adenoviral E3 DNA sequence... preferably all of the E3 region are included in the vector, except the gene encoding the 11.6 Kda protein that causes cell lysis." (See p. 8, lines 6-34; and e.g. Figure 34).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to combine the teachings of Welling and Kadan to make a modified recombinant adenoviral vector comprising modifications of the E2, E4 and E3 gene regions and a nucleic acid encoding an inhibitor of IL-1beta, such as IL-1Ra/IRAP, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to combine the references and create the claimed vector because Kadan clearly indicates that the E2/E3/E4 modified adenoviral vector is an improved adenoviral vector that has been modified to reduce the host immune and inflammatory responses to the vector.

21. Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Welling et al. (Human Gene Therapy 7:1795-1802; 1996) in view of Liu et al. (Hum. Gen. Therp. 7:1719-1726; 1996).

Claim 23 is drawn to a recombinant herpes simplex viral (HSV) vector comprising a nucleic acid sequence encoding IL-IRa (also known as IRAP).

Welling teaches an adenoviral vector comprising a nucleic acid sequence encoding an inhibitor of IL-1beta activity wherein the inhibitor of IL-1beta activity is IL-1Ra (also known as IRAP) (for example seep. 1795 abstract). Welling indicates that the vector was capable of delivering and expressing IL-1Ra in rat skeletal muscle capillary endothelium and muscle fibers during vascular isolation of the hindlimb (see p. 1795, first column). Welling also teaches that IL-1Ra is "a clinically important inhibitor of IL-1's deleterious actions in shock, inflammation and rheumatoid arthritis." (See p. 1796, second column). Welling also indicates that "adenoviral transduction of the lung and liver is associated with an inflammatory reaction with a lymphocytic infiltrate and necrosis" (See p. 1800, second column); and "Transient IL-1Ra expression might be applicable to the prevention of sepsis-induced acute respiratory distress syndrome or multiple organ dysfunction in which IL-beta is critical to disease pathogenesis" (see p. 1801, first column).

Welling does not teach that the IL-1beta inhibitor (IL-1Ra/IRAP) is cloned into a recombinant herpes simplex viral vector.

Liu teaches a recombinant herpes simplex viral vector that is useful for delivering an inhibitor of IL-1beta activity (specifically, Bcl-2) to mammalian beta cells (e.g., see p. 1719, abstract). Liu indicates that the vector can be used to deliver and express an inhibitor of cytokine-induced apoptosis, which results in the reduction of cytokine-induced apoptosis.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to combine the teachings of Welling and Liu to make a recombinant herpes simplex viral vector comprising an inhibitor IL-1Ra with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to combine the references and create

a recombinant HSV vector encoding and expressing IL-1Ra/IRAP in order to reduce the effects of cytokine induced apoptosis.

22. Claims 21 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Welling et al. (Human Gene Therapy 7:1795-1802; 1996) in view of Koeberl et al. (PNAS 94:1426-1431; 1997).

Claim 21 is drawn to an adeno-associated viral vector (AAV) comprising a nucleic acid sequence encoding an inhibitor of IL-1beta activity. Claim 23 is drawn to the vector of claim 21 wherein the inhibitor of IL-1beta activity encoded by the nucleic acid is IL-IRa (also known as IRAP).

Welling teaches an adenoviral vector comprising a nucleic acid sequence encoding an inhibitor of IL-1beta activity wherein the inhibitor of IL-1beta activity is IL-1Ra (also known as IRAP) (for example seep. 1795 abstract). Welling indicates that the vector was capable of delivering and expressing IL-1Ra in rat skeletal muscle capillary endothelium and muscle fibers during vascular isolation of the hindlimb (see p. 1795, first column). Welling also teaches that IL-1Ra is "a clinically important inhibitor of IL-1's deleterious actions in shock, inflammation and rheumatoid arthritis." (See p. 1796, second column). Welling also indicates that "adenoviral transduction of the lung and liver is associated with an inflammatory reaction with a lymphocytic infiltrate and necrosis" (See p. 1800, second column); and "Transient IL-1Ra expression might be applicable to the prevention of sepsis-induced acute respiratory distress syndrome or multiple

organ dysfunction in which IL-beta is critical to disease pathogenesis" (see p. 1801, first column).

Welling does not teach that the IL-1beta inhibitor (IL-1Ra/IRAP) is cloned into an adeno-associated viral vector.

Koeberl teaches an AAV vector that is useful for delivering and expressing a gene of interest to liver cells. Koeberl indicates that the AAV vector has the potential for targeted gene transduction of the liver for treatment of various hematological or metabolic diseases.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to combine the teachings of Welling and Koeberl and make an AAV vector comprising an inhibitor of IL-1beta, specifically IL-1Ra/IRAP, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to combine the references and create an AAV vector encoding and expressing IL-1Ra/IRAP in order to treat inflammation in the liver or liver dysfunction associated with IL-1.

23. Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Welling et al. (Human Gene Therapy 7:1795-1802; 1996) in view of Naldini et al. (PNAS 93:11382-11388; 1996).

Claim 24 is drawn to a lentiviral vector comprising a nucleic acid sequence encoding an inhibitor of IL-1beta activity.

Welling teaches an adenoviral vector comprising a nucleic acid sequence encoding an inhibitor of IL-1beta activity wherein the inhibitor of IL-1beta activity is IL-1Ra (also known as IRAP) (for example seep. 1795 abstract). Welling indicates that the vector was capable of

delivering and expressing IL-1Ra in rat skeletal muscle capillary endothelium and muscle fibers during vascular isolation of the hindlimb (see p. 1795, first column). Welling also teaches that IL-1Ra is "a clinically important inhibitor of IL-1's deleterious actions in shock, inflammation and rheumatoid arthritis." (See p. 1796, second column). Welling also indicates that "adenoviral transduction of the lung and liver is associated with an inflammatory reaction with a lymphocytic infiltrate and necrosis" (See p. 1800, second column); and "Transient IL-1Ra expression might be applicable to the prevention of sepsis-induced acute respiratory distress syndrome or multiple organ dysfunction in which IL-beta is critical to disease pathogenesis" (see p. 1801, first column).

Welling does not teach that the IL-1beta inhibitor (IL-1Ra/IRAP) is cloned into a recombinant lentiviral vector.

Naldini teaches a recombinant lentiviral vector that is useful for delivering and expressing a gene of interest in brain cells in vivo and indicates that the vector may be used to deliver a therapeutic gene product to a wide variety of somatic tissues in vivo (see p. 11382, abstract and paragraph bridging columns 1 and 2).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to combine the teachings of Welling and Naldini to make a recombinant lentiviral vector comprising an inhibitor of IL-1beta, specifically IL-1Ra/IRAP, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to combine the references and create a recombinant lentiviral vector encoding and expressing IL-1Ra/IRAP in order to treat inflammation in the brain or other organ/tissue dysfunction associated with IL-1.

Conclusion

No claim is allowed.

At least one of the rejections above was not necessitated by amendment; therefore, this Action is NON-FINAL.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell
December 13, 2002

DAVE T. NGUYEN
PRIMARY EXAMINER